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RESEARCH NEEDS BASIC TO THE IMPROVEMENT OF NUTRITION AND HEALTH AND
FOR THE PROMOTION OF HUMAN DEVELOPMENT IN THE WESTERN HEMISPHERE

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RESEARCH NEEDS BASIC TO THE IMPROVEMENT OF NUTRITION AND HEALTH AND FOR THE PROMOTION OF HUMAN DEVELOPMENT IN THE WESTERN HEMISPHERE

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by

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Introductory remarks

In the preindustrial areas of the Western Hemisphere, as elsewhere, malnutrition and communicable diseases rank high as public health problems. These two pervasive and interactive problems are inhibiting economic progress in Latin America and the Caribbean through their negative effects on the development of current and perhaps future generations.

We are concerned in several countries of this Hemisphere about population growth rates that exceed rates of expansion in agricultural production, economics growth and social programs. These circumstances unless brought into balance can only lead to increased inequities in the distribution of benefits to those most in need. Forced population control measures for the poor among whom birth rates are highest are unacceptable intervention strategies. Voluntary population control is associated in several countries with reduced infant and childhood mortality as a result of improved equity in the distribution of social and economic benefits.

The Inter-American Investigation of Mortality in Childhood clearly identified nutritional deficiency as the most serious health problem associated with high death rates among children (1). Moreover, nutritional deficiencies were synergistically related to infectious diseases and to complications of pregnancy and childbirth. Of the approximately 300 million people in Latin America and the Caribbean, about 35 percent or 105 million are among the nutritionally vulnerable "at risk" group of children under 5 years (15 percent) and women in the reproductive years (20 percent). Added to this are at least another 60 million constituting the male component of the work force 15-44 years of age whose productivity may
be limited by chronic undernutrition (2). These figures undoubtedly are conservative estimates of the magnitude and seriousness of the problem confronting the Western Hemisphere. Eliminating poverty would go far toward eradicating malnutrition and its attendant consequences. This should be the ultimate goal, but will take years to achieve. In the interim the prevalence of malnutrition can be reduced by appropriately designed intervention programs. The design of such programs and their likelihood of success will be greatly enhanced if founded on knowledge from basic research relevant to the nutritional problems that exist locally.

In this paper I will attempt to address those nutritional problems of the Western Hemisphere of public health concern and to highlight areas in need of research to fill in gaps in our theoretical understanding of the problems and in our ability to intervene and provide solutions.
The Nutritional Problem

Surveys conducted throughout the Western Hemisphere clearly show that calories and protein, iron, vitamin A, folic acid and, in certain areas, iodine are nutrients frequently in short supply and often associated with clinical symptoms (2). Hence, retarded prenatal and postnatal growth, anemia, xerophthalmia and blindness and endemic goiter and cretinism are recognized human nutrient-related health problems. With the exception of growth retardation, these clinical entities appear only after a prolonged intake of an inadequate diet has depleted body reserves and led to a critically diminished supply to cells where they participate in specific essential biochemical reactions. The consequences of acute nutrient deficiencies have been extensively studied; the consequences of subclinical deficits are less precisely known. Acute deficiencies affect a relatively limited proportion of the human population whereas chronic subclinical deficiencies affect many, particularly the rural poor.

The extensive research conducted on animal models have provided insight into the specific role of the nutrients in cellular metabolism and the consequences of imbalances. Many basic questions, however, remain unanswered and studies in animals deserve continued support. For example, apart from the well-recognized role of vitamin A in formation of visual pigments, no other specific biochemical role has been clearly demonstrated even though deficiency results in reproductive failure, growth arrest, inefficient protein metabolism, loss of integrity of epithelial tissue, bone changes, an increased susceptibility to infections and other symptoms. Many of these symptoms of vitamin A deficiency in animal models have parallels in human populations known to have inadequate intakes of vitamin A.
Similarly, carefully controlled studies on pregnant animals have shown that during the gestational period deficits of calories, protein, iron, vitamin A, folic acid, iodine and other nutrients have teratogenic effects, result in pregnancy wastage or low birth weight offsprings, and may irreversibly inhibit certain developmental processes. Again, among undernourished human populations parallel observations are made. But, although animal studies are suggestive these cannot be causally associated with specific nutrient deficiencies in humans living under natural conditions; neither can they be ignored.

For obvious pragmatic and ethical reasons controlled prospective study of specific nutrient deficiencies or excesses possible in animal models cannot be replicated in humans. Rather, in most cases correlation studies must suffice to suggest those nutrients and environmental factors that significantly contribute to observable health problems. Carefully designed correlation studies have shown the characteristics of a population with a low level of nutrition to include at least a high prevalence of low birth weight babies, of infant and childhood mortality and morbidity, of growth retardation and of a reduced work productivity. Also characteristic of the human circumstance is the concurrent occurrence of multiple nutrient deficits so that it is difficult to assign causality to a single nutrient or to expect dramatic positive results from narrowly programmed nutrient intervention schemes.

Nutrition and pregnancy outcome. Malnutrition and infection during the gestational period have acute and chronic consequences for both mother and offspring. Some of these effects, behavioral as well as physiological, are well documented in animal studies with respect to calorie and/or protein malnutrition. They are less well documented in pregnant women
exposed to chronic undernutrition with respect to at least calories, protein and iron and likely folic acid, vitamin A and other vitamins and minerals as well.

Reliable data on the prevalence of pregnancy wastage are not available for the Western Hemisphere. Undoubtedly, however, the figure is high particularly among poor women consuming inadequate diets to support growth of the products of conception (3). Malnourished pregnant women living in the unsanitary stressful environment characteristic of the poor also are likely to have repeated infections (4). The combination of maternal malnutrition and infections contributes in a major way to pregnancy wastage (1). Repeated pregnancy wastage drains maternal nutrient reserves which because of the chronicity of marginal subsistence among the poor are unlikely to be restored before conception is repeated. This vicious cycle presumably accounts for much of the high maternal mortality and shortened life span of this economically deprived group and of the high death rate among their infants (1). Additional data are needed to more adequately document the relation between pregnancy wastage and maternal weight gain (or lack thereof), nutritional status, immune response and maternal infection.

Reliable data in the Western Hemisphere is not available on the proportion of infants born small for gestational age (2500 gm or less). Some studies report a prevalence in excess of 30 percent (5). Low birth weight (LBW) infants do poorly postnatally, frequently die and if they survive often exhibit abnormal social behavior and subnormal psychological testing (5, 6).
Chronic malnutrition and recurrent infections among women before and during gestation characterize environments with a high prevalence of LBW infants. High priority should be given to basic research that precisely identifies the nutritional status and infection history of high-risk mothers and the mechanism through which these insults influence pregnancy outcome. For example, the effects may be through a restricted development of the vascular bed supplying the uterus and placenta, through an altered exchange of nutrients and/or toxicants across the maternal-fetal barrier or through a direct effect of nutrient/toxicants on the developing fetus. Obviously animal models have to be used for definitive prospective studies. However much might be learned from studies of placenta from women delivering LBW infants whose nutritional status can be documented at the time of delivery. By combining this information with retrospective dietary and health histories, village counterparts could be identified for study who are consuming similar home diets and at earlier stages of gestation.

Priority should be given to further describing maternal attributes and practices and associated environmental factors that contribute significantly to the prevalence of LBW infants. Hence, there is need to establish throughout this Hemisphere a recording system for birth weights using a standardized methodology. Such a system should be immediately implemented in institutional settings. Most births, however, occur outside institutions and imaginative programs will be needed to establish monitoring systems in non-institutional settings. The difficulty in establishing systems for obtaining these data should not deter efforts because of the magnitude of the problem and the significance of its consequences to human and social development. A geographic mapping of the
prevalence of the LBW problem would provide the basis for establishing appropriate targeted interventions.

Maternal requirements for nutrients need to be determined for the typical stressful environmental conditions of rural living in Latin America. The aim should be to determine the minimal need to produce an infant of adequate birth weight. Klein et al (7) recently reported that a caloric adjunct of 125 Kilocalories daily supplied prenatally to rural Guatemalan mothers and postnatally to the mother or directly to the child halved the proportion of LBW infants, reduced infant mortality and decreased the prevalence of physical growth retardation among children up to 36 months of age. The caloric adjunct was positively associated with improved psychological test performance as well. No further improvement was noted by providing a protein supplement to this population whose home diet already was adequate in the ratio of protein to calories. Other results might be expected in populations with less adequate protein intakes. For example, using anthropometric measurements of Peruvian mothers, Frisancho et al (8) showed that increased maternal calorie reserves (body fatness) correlated with increased birth weight but increased maternal protein reserves (muscle mass) were needed to enhance both birth weight and prenatal linear growth.

Health and agricultural planners need information on typical home dietary patterns found throughout the Western Hemisphere to design relevant and economically feasible intervention programs and for long range development planning. It is not reasonable to believe that nations with limited capital to invest in health and social programs can provide immediately a nutritionally adequate diet for all or even for the pregnant poor, although this should be a long range goal. It is important therefore
through research to determine the minimal nutritional requirement to support a successful pregnancy outcome. This is a realistic planning goal.

The Inter-American Investigation of Mortality in Childhood revealed an excessive number of deaths from congenital anomalies of the nervous system (1). Research is needed to determine if a causal relationship exists between these anomalies and maternal malnutrition, infection, dietary patterns or other environmental factors. This research should seek through correlation studies to determine the possible causality of specific nutrient imbalances, dietary patterns such as alcohol consumption, potential environmental toxicants, and the combined effects of multiple contributing factors within the ecologic context in which congenital anomalies are highly prevalent. Seldom are pregnant women acutely deficient, for example, only in vitamin A or iron or folic acid but usually they are concurrently depleted in these nutrients while exposed to multiple environmental stresses. The possible synergism of these effects on organogenesis and fetal development during critical periods of gestation should be studied. Once again, research in animal models will play a key role in elucidating the effects and mechanisms of these interactions during fetal development.

One could continue to list a number of specific basic research needs to answer questions regarding the relationship of maternal malnutrition, fetal development and low birth weights. Similar basic research needs could be listed relating infection and other environmental factors that impact on pregnancy outcome. The more general point, however, is that there is priority need for basic investigations into the complex etiology of LBW. Such investigations in the context of the Western Hemisphere are
needed to guide design of appropriate cost effective health intervention programs. However, where intervention programs can be instituted these should not be delayed awaiting definitive results from basic research since it is quite clear that nutritional deficiencies and infections during gestation are major contributors to the high prevalence of pregnancy wastage, low birth weight infants and neonatal and postnatal mortality.

**Nutrition and infection.** Diarrheal disease and measles are of first and second importance as the principle causes of death in Latin American children (1). The evidence for a synergistic relationship between nutrition and infectious diseases reviewed by Scrimshaw et al in 1968 (9) has since been substantiated in part by studies in animal models and in *vitro* systems. These model systems have elucidated the specific role of some nutrients particularly protein and iron, and perhaps vitamin A in both the cellular and humoral immune systems. The studies in malnourished children have been less clear and should receive priority consideration because of the predominance of malnutrition and infectious diseases as causes of childhood mortality.

The research design for studies of the immune response of the malnourished child requires that nutritional status, immune status and infection history be quantitatively documented, monitored and evaluated from an interrelated causality perspective (10). Field research in naturalistic settings with this degree of precision will be difficult to design and carry out and for ethical reasons must include therapeutic interventions where clinically warranted. The studies should be longitudinal where possible to differentiate between transient and permanent consequences of various forms and degrees of severity of malnutrition.
Pregnant women as well as young children should be studied because of evidence suggesting that infections during the gestation period in malnourished women can influence pregnancy outcome and postnatal growth (4, 5).

When clinical studies of a basic research nature are conducted in man under no circumstances should treatment be withheld. Therapeutic intervention must be given for obvious ethical reasons. Nonetheless, data collected when subjects are seen initially should be presented and evaluated in terms of their temporal relationship to the onset of disease as well as to the initiation and course of therapy. Here again there is need to study the role played by malnutrition and infection during the gestational period and their effect on the immune system of the offspring.

The importance of breast-feeding to neonatal immunity should be investigated and the function of secretory immunoglobulins and maternal macrophages in milk defined. Puffer and Serrano (1) recorded a remarkably higher death rate in the first year for infants not breast fed or breast fed only for one month. They also recorded the alarming fact that in some countries of the Western Hemisphere about 50-75 percent of newborns receive breast milk for only a month whereas the general belief had been that breast feeding for longer periods is the usual method of feeding infants in Latin America. In this regard, there is need for research on why breast feeding is of short duration, for social or physiological reasons. If physiological, then what is the effect of environmental stresses on success in breast feeding or what other factors might be involved. Priority should be given to research on breast feeding practices since deaths from diarrheal disease and nutritional deficiency was less in infants breast fed for longer periods.
Nutritional anemia. Iron deficiency is the most prominent cause of anemia worldwide (11). In the Western Hemisphere iron deficiency is frequently accompanied by deficiency of folic acid (2) a nutrient also causally related to a decreased synthesis and maturation of erythrocytes by bone marrow. Both of these nutrients may be inadequately supplied to tissues due to dietary deficiency or to a limited availability from foods. It is not infrequent to find populations whose diets contain adequate iron and/or folic acid, but due to other dietary constituents, storage or cooking procedures and perhaps decreased intestinal enzyme activity or mucosal atrophy, the nutrients are not effectively available or absorbed. Doctor Layrisse and others have made significant fundamental contributions in developing a methodology for determining iron availability from natural diets (12). This methodology needs to be applied in humans residing in geographic areas in the Western Hemisphere where anemia is highly prevalent. Concurrent information on cultural food patterns and intestinal parasitism should be sought as a basis for determining appropriate intervention alternatives. For example, it will be of limited utility to provide an iron supplement through a fortification program if the characteristics of the local diet are such as to negate the availability of the supplemental iron. On the other hand, knowledge of local dietary patterns may allow for slight modifications through nutrition education that could lead to permanent improved availability of dietary iron. For example, a recent report indicates that the simultaneous ingestion of iron and ascorbic acid-rich foods enhances absorption efficiency and decreased the prevalence of anemia (13). Through basic research naturally occurring foods that may act as iron absorption enhancers should be sought.
Research is needed to precisely define the detrimental effects of mild anemia and of latent deficiencies of iron and folate without anemia. Recent evidence suggests that human work performance is affected by even mild anemia (11) and as such can have important consequences for economic progress. Additionally some evidence exists that iron deficiency may influence cellular and humoral immunity and alter the functioning of granulocytes (11). There is need to determine using recently developed methodologies the level of iron nutriture that is associated with a compromise in function and work productivity. These studies should consider both the effects of iron deficiency singly and combined with inadequate intakes of vitamin A, folate, protein and calories. These other nutrients may act synergistically to effect outcomes and if so, must be considered in the design of intervention programs to reach population groups in which multiple nutrients deficits are the rule rather than the exception.

The food industry and other appropriate institutions in the Western Hemisphere should be encouraged to do basic research on culturally acceptable vehicles that might act as effective carriers of iron for fortification programs. These studies must consider the form of iron most stable and physiologically available from these vehicles within the context of village storage, preparation, and consumption conditions. These studies should also seek vehicles with potential for effectively carrying more than a single nutrient to "at risk" populations since commonly these groups suffer from multiple nutrient deficits.

Although iron deficiency is the primary cause of anemia in Latin America, folic acid deficiency, and to a lessor extent vitamin B₁₂, contribute to the problem especially in pregnant women (2). Because iron
deficiency can mask the presence of concurrent folate deficiency, research is needed to differentiate between the two nutrients as the cause of anemia. This can best be done by therapeutic supplementation trials. Where folate deficiency occurs, there is need for research to determine cause. Food storage and cooking procedures can destroy significant amounts of folate in foods. Alteration in local food handling where such practices exist could be the most effective long-range solution to the problem.

Hypovitaminosis A. An inadequate dietary intake of vitamin A and a high prevalence of low serum levels is reported for populations in several countries in the Western Hemisphere (2). Young children are those most severely affected and in whom irreversible blindness may occur, especially associated with protein-calorie malnutrition. The biochemical role of vitamin A in formation of visual pigments is understood. The vitamin's role in other vital physiological processes remains enigmatic despite extensive research efforts (15).

Vitamin A in animals is unquestionably related to growth, normal cellular differentiation, resistance to infection and normal reproduction. Yet in humans there are no well-authenticated studies that unquestionably demonstrate a health benefit, other than those associated with the eye, from providing supplements to diets chronically low in vitamin A. Most field studies attempting to relate subclinical vitamin A nutrition to morbidity have used a simplistic, single nutrient, cause/effect approach. Most have not critically determined the relative nutritional status of subjects with respect to several other nutrients also known to relate to resistance to infection and to influence immune responses. For these types of morbidity studies anthropometric measures and/or clinical observations are not adequate indicators of nutritional or immune
status. Therefore, there is need for research to relook with precision in young children at the interrelationship between infection and chronic undernutrition from the multicausality framework characteristic of village settings.

There is currently no practical way of determining relative tissue status of vitamin A in living children. Most of the vitamin is stored in the liver and serum values are maintained in the normal range until the liver reserves are depleted. Obviously liver biopsies cannot be done in the field. Distribution curves for serum vitamin A by age groups from large populations of subjects are suggestive of the magnitude of the problem. Serially obtained curves of serum vitamin A are useful to monitor improvements resulting from intervention such as the vitamin A sugar fortification program now in progress in some Central and South American countries (16). Clinical surveys are time consuming and only detect the tip of the iceberg, the end of the depletion spectrum. Dietary surveys on young children are unreliable and not feasible in large numbers. Hence, although there is need for greater precision in identifying populations and "pockets" of high prevalence of deficiency, there is no simple inexpensive way of doing so.

Health planners and politicians must rely on serum distribution curves, clinical signs seen in medical institution settings and some knowledge of ecologic and economic factors generally associated with the occurrence of deficiency to guide decisions justifying intervention programs (17). Importantly, they must also be guided by the evidence from animal studies not replicable in humans of multiple health benefits from adequate vitamin A nutriture. Considering these factors intervention programs to improve vitamin A intakes should be considered for several countries in the
Western Hemisphere with evidence of a problem of inadequate dietary intakes. Fortification of a suitable food or foods is the most practical and least expensive intervention approach. There is need for research to identify appropriate food sources which could be fortified and reach vulnerable population groups in Western Hemisphere countries (18). This research must include sociocultural consideration of food practices and typical home food preparation procedures. Sugar is an effective vehicle for Guatemala, Costa Rica and likely other countries of the region. Other potential carriers should be sought.

Recent work in animals and correlation studies in humans suggests that the efficient utilization of iron for hemoglobin synthesis is influenced by concurrent vitamin A deficiency (19). The potential importance of this interrelationship to improvement of human health and nutrition in the Western Hemisphere where both nutrients are in short supply is enormous. Research is needed to confirm if indeed a relationship exists and if so the relative levels of deficit before functional consequences occur.

Vitamin A affects epithelial cell differentiation, different tissues having differing thresholds at which a squamous epithelium in deficiency or an accumulation of goblet cells in excess is observed. Epithelial integrity is a first line of defense in resistance to infectious agents. In part this defense is also dependent on production of glycoprotein-containing mucoid secretions by goblet cells and perhaps of macroglobulins by the liver. Recent reports from animal studies have linked vitamin A to glycoprotein synthesis and more specifically to a vitamin A response glycoprotein-containing $\alpha_1$-macroglobulin in serum (19). There is need to examine levels of this macroglobulin in populations of "at
risk" children and to seek correlations with vitamin A status, infection resistance and development of keratomalacia.

**Endemic goiter and cretinism.** Endemic goiter occurs in many Latin American countries particularly in the Andean and other mountainous regions (14). It is now generally agreed that the most important single factor causally related to endemic goiter is an inadequate dietary intake of iodine. A mildly enlarged thyroid in adults may have only cosmetic significance but severe goiter can obstruct passageways. Endemic goiter has been associated epidemiologically with cretinism and deaf-mutism. Those so severely effected by this preventable but irreversible tragedy become unproductive emotional and economic burdens for families and society. Fortunately, with few exceptions the prevalence of cretinism does not appear to be high in most countries of the Western Hemisphere. From a public health view, however, a prevalence of 5% endemic goiter among adolescent girls is indicative of an area where iodine intakes are inadequate to meet the needs of the thyroid gland at least at some stage during development. Endemic goiter at this level occurs in several countries of the Hemisphere (1, 12-pg. 242). There is some data that suggest that suboptimal iodine levels may be related to impaired thyroid function and a decreased mental performance among noncretinous populations (12-p.8, 135). However, the health consequences of chronic low intakes is not unquestioned. Basic research is needed to clarify the short and long term functional significance of chronic subclinical iodine intakes at different critical stages of development, particularly during gestation (12-pg. 143).

**Other nutrition-related diseases.** Limited data are available on the prevalence of other possible nutrient-related diseases in the
Western Hemisphere (2). For example, little is known about the level of trace minerals other than iron, such as zinc and copper which could be contributing to anemia and other forms of inefficient physiological functions that compromise health. Also there is limited data on the prevalence of nutrition-related diseases that usually accompany rising affluence and technological development, such as cardiovascular disease, diabetes and cancer. Epidemiologic research is needed to establish now the magnitude of these problems in Latin America and the Caribbean in order to monitor changing patterns of prevalence that might be expected to accompany future economic development. Hopefully such a monitoring system could trigger preventive programs to ward off these diseases before reaching the magnitude seen today in the United States and Canada.
Summary -

Briefly this paper identifies five broad areas in which basic research is needed over the next several years to improve nutrition and health and to promote human development in the Western Hemisphere. These five areas include the relationship between nutrition and pregnancy outcome, nutrition and infection, nutritional anemias, hypovitaminosis A and endemic goiter and cretinism. General directions research into these areas might take are suggested but no attempt is made to comprehensively list all the possibilities. Underlying the discussion are four general themes:

1. that human nutrition/health problems in natural settings have a multicausal etiology;

2. that research in animal models is needed to specifically delineate the role of nutrients and their interrelationships at the cellular level;

3. but that human field research designed and evaluated from a multicausal perspective is necessary to correlate this basic information with its functional consequences for human development;

4. from such a research base, appropriate interventions can be designed to minimize human suffering and improve the quality of life for all in the Western Hemisphere.
References:


